REMARKS

Applicants note that the Examiner indicates that the request for filing a Continued Prosecution Application (CPA) under 37 CFR 1.53(d), based on parent Application Ser. No. 09/462,846 has been accepted. Applicants further note that the election of the Claims in Group I (Claims 1, 4-9, and 13-17) made in the Response dated April 20, 2001, has been recorded. Thus, Claims 1, 4-9, and 13-17 were pending in the present application. Applicants have added dependent Claims 18-21 in the present Response. Thus, Claims 1, 4-9, and 13-21 are currently pending.

Applicants note that a Patent Office Draftsperson has not reviewed the drawings filed in the present case. Upon notification, Applicants will file any revised drawings needed.

Applicants also note that the Examiner has objected to the title of the application. Applicants appreciate the Examiner's suggestion for amending the title. Although Applicants believe that the title is sufficiently descriptive as filed, Applicants have amended the title to indicate that the application is directed toward Gram-positive microorganisms with inactivated cysteine protease 1 (CP-1) enzymes. Support for this amendment is found in the Specification (*i.e.*, the genus *Bacillus* contains Gram-positive organisms).

Applicants further note that the Examiner has objected to Claims 4, 6-8, as being dependent upon non-elected Claims 2 and 3. Applicants have amended Claims 4 and 6, in order to recite the correct dependency.

The Examiner has also objected to Claims 13 and 16, as allegedly being drawn to non-elected subject matter. Applicants have amended these Claims without prejudice and reserve the right to prosecute the cancelled subject matter in one or more Divisional or other applications.

The Examiner has further objected to Claims 1 and 15-17, for the recitation of "CP1" in Claims 1 and 16, and "apr," "npr," "epr," "wpr," and "mrp"

(this should be "mpr") in Claims 15 and 17. Applicants submit that these abbreviations are clear to those of skill in the art and are commonly used as the names of the proteins. However, Applicants note that "apr" is generally used in reference to alkaline protease, and "npr" is generally used in reference to neutral protease. Nonetheless, utilizing the originally designated name for "mpr" would be confusing, as this name is based on the original, incorrect designation of this protein as a metalloprotease. "Mpr" is a member of the S2 family of serine proteases and is *not* a metalloprotease. Thus, Claims 15 and 17 have not been amended, as the recitations of "apr," "npr," "epr," "wpr," and "mpr" are typically used as the names of the proteases. However, if the Examiner so requires, Applicants will amend the Claims to recite "alkaline protease," rather than "apr," and "neutral protease," rather than "npr."

Finally, the Examiner objects to Claims 1, 7, 9, and 16 for various formalities. Applicants have amended these Claims to correct grammatical and typographical errors. No new matter has been added in these amendments.

The Examiners rejections of the Claims are addressed in the order below:

1) Claims 5 and 9 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite;

2) Claims 1, 4-9, and 13-17 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description requirement, nor the enablement requirement; and

3) Claims 1, 4-9, and 13-17 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by WO 89/10976.

1) The Claims Are Definite

The Examiner has rejected Claims 5 and 9 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. In particular, the Examiner states that Claim 5 is confusing in its recitation of various *Bacillus* species and Claim 9 is unclear in its *Markush* recitation. Applicants have amended Claims 5 and 9

without prejudice, in order to more clearly define the claimed invention. Applicants believe that the Claims are in condition for allowance and respectfully request that this rejection be withdrawn.

2) The Present Specification and Claims Meet the Written Description and Enablement Requirements

The Examiner has rejected Claims 1, 4-9, and 13-17 9 under 35 U.S.C. §112, first paragraph, as allegedly not meeting the written description and enablement requirements. More particularly, the Examiner indicates that the Claims are drawn to a genus of cysteine protease 1 (CP1) genes, with any structure and from any source. Applicants note that the Examiner admits that the Specification teaches mutant cysteine protease 1 from *Bacillus subtilis* (SEQ ID NO:1), which results in inactivation of CP1 activity, as well as methods for producing heterologous proteins in host cells. The Examiner argues that teaching one representative species is not enough to describe the whole genus and there is no evidence of the relationship between the structure of *B. subtilis* CP1 and the structure of a CP1 from another Gram-positive organism.

In regards to enablement, the Examiner argues that the rejected Claims (Claims 1, 4-9, and 13-17) "are so broad as to encompass *any* gram-positive microorganism, *any* Bacillus, [sic] or *any* of the Bacilli [sic] listed in claim 5 having *any* mutation or deletion of any gene encoding CP1 resulting in the inactivation of CP1 proteolytic activity . . . ." (Office Action, page 5, emphasis original). However, Applicants note that the Examiner admits that the present Specification is enabling for *B. subtilis* host cells with a deletion of the polynucleotide of SEQ ID NO:1, thereby resulting in the inactivation of CP1 proteolytic activity and a method for producing heterologous proteins using the host cells (Office Action, page 5).

Applicants must respectfully disagree with the Examiner's arguments and believe that the Specification as filed meets both the written description and enablement requirements. Nonetheless, in order to further the prosecution of

the present application and their business interests, yet without acquiescing to the Examiner's arguments, Applicants have amended independent Claims 1 and 13 to recite SEQ ID NO:2 (*i.e.*, the amino acid sequence of CP1). Newly added dependent Claims 18-21 recite the nucleic acid sequence of SEQ ID NO:1. Applicants submit that the amended and new Claims are supported by the Specification, and no new matter is introduced by these amendments, nor is there any new matter added in the new Claims. Furthermore, the pending Claims meet the written description and enablement requirements. Applicants respectfully request that this rejection be withdrawn.

3) The Claims are Novel

Claims 1, 4-9, and 13-17 stand rejected under 35 U.S.C. §102(b) as being allegedly anticipated by WO 89/10976. The Examiner argues that WO 89/10976 teaches the inactivation of genes encoding *Bacillus subtilis* cysteine and serine proteases in a neutral and alkaline protease-deficient *B. subtilis* host cell, and the creation of a mutant *B. subtilis* strain that is deficient in all four proteases (cysteine, serine, alkaline, and neutral protease) activities (Office Action, page 8). Applicants must respectfully disagree.

WO 89/10976 teaches a *B. subtilis* strain that is deficient in **both** alkaline protease and neutral protease, as well as sulfhydrl-dependent *residual* cysteine protease and/or a *residual* serine protease activities. These residual proteases are described as providing residual protease activity in *Bacillus* strains that are apr^-/npr^-, and are responsible for the degradation of proteins in cultures of *B. subtilis*. There is no teaching in WO 89/10976 of an organism with a mutation or deletion of part or all of the gene encoding CP-1. Likewise, there is no teaching in WO 89/10976 of an organism with such a mutation or deletion in CP-1, as well as mutation(s) and/or deletion(s) in at least one of the genes encoding apr, npr, epr, wpr, and/or mpr. Indeed, there is no teaching in WO 89/10976 of the CP1 of the presently claimed invention. Thus, WO 89/10976 does not teach each

and every element of the Claims[1], a requirement for a reference to be anticipatory. Nonetheless, in order to further the prosecution of the present application and Applicant's business interests, the independent Claims have been amended to recite SEQ ID NO:2. New Claims 18-21 include the sequence of SEQ ID NO:1. These amendments and new Claims find support in throughout the Specification and do not introduce new matter. Applicants respectfully request that this rejection be withdrawn and the Claims passed to allowance.

CONCLUSION

All grounds of rejection and objection of the Office Action of January 22, 2002, having been addressed, reconsideration of the application is respectfully requested. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicants encourages the Examiner to call the undersigned.

Respectfully submitted,

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[1] "Anticipation is established only when a single prior art reference discloses, expressly or under principles of inherency, each and every element of a claimed invention." *RCA Corp. v. Applied Digital Data Sys., Inc.*, 730 F.2d 1440, 221 USPQ 385, 388 (Fed. Cir. 1984).

APPENDIX I
MARKED-UP VERSION OF SPECIFICATION'S REPLACEMENT PARAGRAPHS AND REWRITTEN, ADDED, AND/OR CANCELLED CLAIMS

The following is a marked-up version of the Specification's replacement paragraphs pursuant to 37 C.F.R. §1.121(b), as well as a marked-up version of the Claims pursuant to 37 C.F.R. §1.121 (c)(1)(ii) with instructions and markings showing changes made herein to the previous version of record of the specification and claims. Underlining denotes added text while bracketing denotes deleted text.

IN THE TITLE

Please replace the originally filed Title with the new Title, as below:

[Proteases from Gram-Positive Organisms]

Gram-Positive Microorganisms with Inactivated Cysteine Protease-1

IN THE CLAIMS:

1. (Amended) A gram-positive microorganism having a mutation or deletion of part or all of the gene encoding cysteine protease-1 CP1, wherein said gene encodes the amino acid sequence set forth in SEQ ID NO:2, and said mutation or deletion [resulting] results in the inactivation of the CP1 proteolytic activity.

4. (Amended) The gram-positive microorganism according to Claim[s]1[, 2 or 3] that is a member of the [family] genus *Bacillus*.

5. (Amended) The microorganism according to Claim 4, wherein the member is selected from the group consisting of *B. subtilis*, *B. licheniformis*, *B. lentus*, *B. brevis*, *B. stearothermophilus*, *B. alkalophilus*, *B. amyloliquefaciens*, *B. coagulans*, *B. circulans*, *B. lautus*, [*and Bacillus*] and *B. thuringiensis*.

6. (Amended) The microorganism of Claim 1[, 2 or 3] wherein said microorganism is capable of expressing a heterologous protein.

7. (Amended) The microorganism of Claim 6, wherein said heterologous protein is selected from the group consisting of hormones, enzymes, growth factors, and cytokines.

8. The microorganism of Claim 7 wherein said heterologous protein is an enzyme.

9. (Amended) The microorganism of Claim 8 wherein said enzyme is selected from the group consisting of [a] proteases, carbohydrases, [and] lipases,[;] isomerases, [such as] racemases, epimerases, tautomerases, [or] mutases[;] transferases, kinases and phosphatases.

13. (Amended) A method for the production of a heterologous protein in a *Bacillus* host cell comprising the steps of:

(c) obtaining a *Bacillus* host cell comprising nucleic acid encoding said heterologous protein wherein said host cell contains a mutation or deletion in at least one of the genes encoding cysteine protease 1, [cysteine protease 2 and cysteine protease 3], wherein said at least one of the genes encoding cystein protease 1 encodes the amino acid sequence set forth in SEQ ID NO:2; and

(d) growing said *Bacillus* host cell under conditions suitable for the expression of said heterologous protein.

14. (Amended) The method of Claim 13 wherein said *Bacillus* cell is selected from the group consisting of *Bacillus subtilis*, *B. licheniformis*, *B. lentus*, *B. brevis*, *B. stearothermophilus*, *B. alkalophilus*, *B. amyloliquefaciens*, *B. coagulans*, *B. circulans*, *B. lautus*, [*and Bacillus*] *B. thuringiensis*.

15. (Amended) The method of Claim 13 wherein said [Bacillus] *Bacillus* host cell further comprises a mutation or deletion in at least one of the genes encoding at least one protease selected from the group consisting of apr protease, npr protease, epr protease, wpr protease and [mrp] mpr protease.

16. (Amended) A gram-positive microorganism having [at] a mutation or deletion in at least one of the genes encoding [a] cysteine protease CP1 [selected from the group consisting of CP1, CP2 and CP3].

17. (Amended) The microorganism of Claim 16, further comprising a mutation or deletion in at least one of the genes encoding at least one protease selected from the group consisting of apr protease, npr protease, epr protease, wpr protease and [mrp] mpr protease.

Please add the following new Claims:

18. (New) The gram-positive microorganism of Claim 16, wherein said at least one of the genes encoding cysteine protease CP1 is set forth in SEQ ID NO:1.

19. (New) The microorganism of Claim 18, further comprising a mutation or deletion in at least one of the genes encoding at least one protease selected from the group consisting of apr protease, npr protease, epr protease, wpr protease and mpr protease.

20. The method of Claim 13, wherein said *Bacillus* comprises the nucleic acid sequence set forth in SEQ ID NO:1.

21. The method of Claim 20, further comprising a mutation or deletion in at least one of the genes encoding at least one protease selected from the group consisting of apr protease, npr protease, epr protease, wpr protease and mpr protease.